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Addressing Parents' Concerns: Do Multiple Vaccines Overwhelm or Weaken the Infant's Immune System?

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ABSTRACT. Recent surveys found that an increasing number of parents are concerned that infants receive too many vaccines. Implicit in this concern is that the infant's immune system is inadequately developed to handle vaccines safely or that multiple vaccines may overwhelm the immune system. In this review, we will examine the following: 1) the ontogeny of the active immune response and the ability of neonates and young infants to respond to vaccines; 2) the theoretic capacity of an infant's immune system; 3) data that demonstrate that mild or moderate illness does not interfere with an infant's ability to generate protective immune responses to vaccines; 4) how infants respond to vaccines given in combination compared with the same vaccines given separately; 5) data showing that vaccinated children are not more likely to develop infections with other pathogens than unvaccinated children; and 6) the fact that infants actually encounter fewer antigens in vaccines today than they did 40 or 100 years ago. *Pediatrics* 2002;109:124–129; *multiple vaccines, immunity, parental concerns.*

ABBREVIATIONS. Ig, immunoglobulins; Th, helper T-cell; Hib, *Haemophilus influenzae* type b; OPV, oral polio vaccine; HIV, human immunodeficiency virus; MMR, measles-mumps-rubella; DTP, diphtheria-tetanus-pertussis.

One hundred years ago, children received 1 vaccine (the smallpox vaccine). Forty years ago, children received 5 vaccines routinely (diphtheria, pertussis, tetanus, polio, and smallpox vaccines) and as many as 8 shots by 2 years of age. Today, children receive 11 vaccines routinely and as

many as 20 shots by 2 years of age (Table 1). The increased number of vaccines given to children and the increased percentage of children receiving vaccines have resulted in a dramatic decrease in the number of vaccine-preventable diseases. Most young parents today have never seen many of the diseases that vaccines prevent. As a possible consequence of these trends, recent national surveys found that 23% of parents questioned the number of shots recommended for their children,¹ and 25% were concerned that vaccines might weaken the immune system.¹

Because most parents receive information and recommendations about vaccines from their doctors,² and because these recommendations carry substantial weight with parents,^{3,4} providers must be knowledgeable when addressing parents' concerns. This article will provide health care professionals with information about the effect of vaccines on the infant's immune system and the capacity of the immune system to respond safely to multiple vaccines.

A BRIEF SUMMARY OF NEONATAL AND INFANT IMMUNE RESPONSES

The Neonatal Immune System

Neonates develop the capacity to respond to foreign antigens before they are born. B and T cells are present by 14 weeks' gestation and express an enormous array of antigen-specific receptors.⁵ Although the fetal immune system has the potential to respond to large numbers of foreign antigens, few foreign antigens are present in utero, and cells of the immune system are, therefore, primarily "naïve" at birth.

Passively Acquired Immunity

The neonate is, in part, protected against disease by maternal immunoglobulins (Ig). Maternal IgG is transported across the placenta before birth and maternal secretory IgA is present in breast milk and colostrum. These passively acquired antibodies provide protection against pathogens to which the mother was immune. However, protection provided by passively transferred antibodies is short-lived. Passively acquired maternal IgG declines during the first few months of life,⁶ and most infants are not breastfed beyond several months of age.⁷ More importantly, maternal antibodies offer limited immunologic protection when compared with protection afforded by an infant's active immune response.

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TABLE 1. Number of Vaccines and Possible Number of Injections Over the Past 100 Years

Year	Number of Vaccines	Possible Number of Injections by 2 Years of Age	Possible Number of Injections at a Single Visit
1900*	1	1	1
1960†	5	8	2
1980‡	7	5	2
2000§	11	20	5

* In 1900, children received the smallpox vaccine.

† In 1960, children received the smallpox, diphtheria, tetanus, whole-cell pertussis, and polio vaccines. The diphtheria, tetanus, and whole-cell pertussis vaccines were given in combination (DTP), and the polio vaccine (inactivated) was given as a series of 3 injections.

‡ In 1980, children received the DTP, polio, and MMR vaccines. The DTP and MMR vaccines were given in combination and the polio vaccine (live, attenuated) was given by mouth.

§ In 2000 children received the diphtheria-tetanus-acellular-pertussis, MMR, inactivated polio, Hib, varicella, conjugate pneumococcal, and hepatitis B vaccines.

Active Immunity

Neonates are capable of generating both humoral and cellular immune responses to pathogens at the time of birth.^{8,9} Active immunity in the newborn includes the full range of B-cell responses including the production of IgM, IgG, and secretory and monomeric IgA, as well as the development of helper T-cell (Th) and cytotoxic T-cell responses.^{8,9} In addition, neonates can produce specific Th-cell subsets, including Th1-type cells that participate in cell-mediated immune responses and Th2-type cells that are primarily involved in promoting B-cell responses.^{8,9}

The development of active humoral and cellular immune responses in the newborn is necessary to meet the tremendous number of environmental challenges encountered from the moment of birth. When children are born, they emerge from the relatively sterile environment of the uterus into a world teeming with bacteria and other microorganisms. Beginning with the birth process, the newborn is exposed to microbes from the mother's cervix and birth canal, then the surrounding environment. Within a matter of hours, the gastrointestinal tract of the newborn, initially relatively free of microbes, is heavily colonized with bacteria.¹⁰ The most common of these colonizing bacteria include facultative anaerobic bacteria, such as *Escherichia coli* and streptococci, and strict anaerobic bacteria, such as *Bacteroides* and *Clostridium*.¹⁰ Specific secretory IgA responses directed against these potentially harmful bacteria are produced by the neonate's intestinal lymphocytes within the first week of life.¹¹

Functional Differences Between Infant and Adult Immune Responses

Although infants can generate all functional T-cells (ie, Th1, Th2, and cytotoxic T-cells),^{8,9} infant B-cell responses are deficient when compared with older children and adults. Infants respond well to antigens (such as proteins) that require T-cell help for development. However, until about 2 years of age, the B-cell response to T-cell-independent antigens (such as polysaccharides) is considerably less than that found in adults.¹² For this reason, infants are uniquely susceptible to bacteria that are coated with polysaccharides (such as *Haemophilus influenzae* type b [Hib] and *Streptococcus pneumoniae*).

IMMUNE RESPONSE TO VACCINES BY NEONATES

The neonate is capable of mounting a protective immune response to vaccines within hours of birth.⁹ For example, neonates born to mothers with hepatitis B virus infection mount an excellent protective immune response to hepatitis B vaccine given at birth, even without additional use of hepatitis B virus-specific immunoglobulin.¹³⁻¹⁵ In addition, BCG vaccine given at birth induces circulating T-cells that protect against bacteremia and subsequent development of military tuberculosis and tuberculous meningitis.¹⁶⁻¹⁸

IMMUNE RESPONSE TO VACCINES BY INFANTS

The young infant is fully capable of generating protective humoral and cellular immune responses to multiple vaccines simultaneously. Approximately 90% of infants develop active protective immune responses to the primary series of diphtheria-tetanus-acellular-pertussis, hepatitis B, pneumococcus, Hib, and inactivated polio vaccines given between 2 months and 6 months of age.¹⁹

To circumvent the infant's inability to mount T-cell-independent B-cell responses, polysaccharide vaccines (Hib and *S pneumoniae*) are linked to proteins (ie, diphtheria toxoid, diphtheria toxin mutant protein, tetanus toxoid, or meningococcal group B outer-membrane protein) that engage the infant's Th-cells. By converting a T-cell-independent immune response to a T-cell-dependent response, conjugate vaccines can be recognized by the infant's B-cells. Conjugate vaccines, therefore, induce protective immune responses in infants that are often greater than those found after natural infection.²⁰

IMMUNE RESPONSE TO VACCINES BY CHILDREN WITH IMMUNODEFICIENCIES

Severely immunocompromised children (specifically, those with T-cell defects) who receive live viral vaccines (eg, measles or varicella vaccines)^{21,22} or live bacterial vaccines (eg, BCG vaccine)^{23,24} may develop disseminated infections with these attenuated pathogens. However, the only live vaccine that was routinely given in the United States in the first year of life, the oral polio vaccine (OPV), has now been replaced with inactivated polio vaccine. Therefore, children do not receive their first live viral vaccines

until about 12 to 15 months of age. Most children with severe T-cell deficiencies (eg, severe combined immunodeficiency syndrome) will have been identified by 6 to 8 months of age.^{24,25}

However, many children with immunodeficiencies respond well to live viral vaccines. Because the risk of severe infection is greater after natural infection with wild-type viruses than immunization with highly attenuated viruses, the Advisory Committee on Immunization Practices and American Academy of Pediatrics recommend that certain immunocompromised children should receive live viral vaccines. For example, children with human immunodeficiency virus (HIV) infection without severe T-cell deficiencies (Centers for Disease Control and Prevention class N1 or A1 and age-specific percentage of CD4⁺ lymphocytes greater than 25%) should receive the measles-mumps-rubella (MMR), and varicella vaccines.^{26–28} Immunizations are well-tolerated by this subset of HIV-infected children and confer protective immunity.^{29,30} Immunization with live viral vaccines has also been demonstrated to be safe and effective in certain children with malignancies and in children following bone marrow transplantation.^{31,32}

IMMUNE RESPONSE TO VACCINES BY CHILDREN WITH MILD, MODERATE, OR SEVERE ILLNESSES

Some parents may be concerned that children with acute illnesses are, in a sense, immunocompromised, and that they are less likely to respond to vaccines or more likely to develop adverse reactions to vaccines than healthy children. Alternatively, parents may believe that children who are ill should not further burden an immune system already committed to fighting an infection. However, vaccine-specific antibody responses and rates of vaccine-associated adverse reactions of children with mild or moderate illnesses are comparable to those of healthy children. For example, the presence of upper respiratory tract infections, otitis media, fever, skin infections, or diarrhea do not affect the level of protective antibodies induced by immunization.^{33–37}

Data on the capacity of vaccines to induce protective immune responses in children with severe infections (such as those with bacterial pneumonia or meningitis) are lacking. Although a delay in vaccines is recommended for children with severe illnesses until the symptoms of illness resolve,²⁶ this recommendation is not based on the likelihood that the child will have an inadequate immune response to the vaccine. Rather, the reason for deferring immunization is to avoid superimposing a reaction to the vaccine on the underlying illness or to mistakenly attribute a manifestation of the underlying illness to the vaccine.²⁶

DO VACCINES “OVERWHELM” THE IMMUNE SYSTEM?

Infants Have the Capacity to Respond to an Enormous Number of Antigens

Studies on the diversity of antigen receptors indicate that the immune system has the capacity to respond to extremely large numbers of antigens.

Current data suggest that the theoretical capacity determined by diversity of antibody variable gene regions would allow for as many as 10⁹ to 10¹¹ different antibody specificities.³⁸ But this prediction is limited by the number of circulating B cells and the likely redundancy of antibodies generated by an individual.

A more practical way to determine the diversity of the immune response would be to estimate the number of vaccines to which a child could respond at one time. If we assume that 1) approximately 10 ng/mL of antibody is likely to be an effective concentration of antibody per epitope (an immunologically distinct region of a protein or polysaccharide),³⁹ 2) generation of 10 ng/mL requires approximately 10³ B-cells per mL,³⁹ 3) a single B-cell clone takes about 1 week to reach the 10³ progeny B-cells required to secrete 10 ng/mL of antibody³⁹ (therefore, vaccine-epitope-specific immune responses found about 1 week after immunization can be generated initially from a single B-cell clone per mL), 4) each vaccine contains approximately 100 antigens and 10 epitopes per antigen (ie, 10³ epitopes), and 5) approximately 10⁷ B cells are present per mL of circulating blood,³⁹ then each infant would have the theoretical capacity to respond to about 10 000 vaccines at any one time (obtained by dividing 10⁷ B cells per mL by 10³ epitopes per vaccine).

Of course, most vaccines contain far fewer than 100 antigens (for example, the hepatitis B, diphtheria, and tetanus vaccines each contain 1 antigen), so the estimated number of vaccines to which a child could respond is conservative. But using this estimate, we would predict that if 11 vaccines were given to infants at one time, then about 0.1% of the immune system would be “used up.”

However, because naive B- and T-cells are constantly replenished, a vaccine never really “uses up” a fraction of the immune system. For example, studies of T-cell population dynamics in HIV-infected patients indicate that the human T-cell compartment is highly productive.⁴⁰ Specifically, the immune system has the ability to replenish about 2 billion CD4⁺ T lymphocytes each day. Although this replacement activity is most likely much higher than needed for the normal (and as yet unknown) CD4⁺ T-cell turnover rate, it illustrates the enormous capacity of the immune system to generate lymphocytes as needed.

Children are Exposed to Fewer Antigens in Vaccines Today Than in the Past

Parents who are worried about the increasing number of recommended vaccines may take comfort in knowing that children are exposed to fewer antigens (proteins and polysaccharides) in vaccines today than in the past.

Table 2 summarizes the number of proteins and polysaccharides contained in routinely recommended vaccines administered over the past 100 years. Although we now give children more vaccines, the actual number of antigens they receive has declined. Whereas previously 1 vaccine, smallpox, contained about 200 proteins, now the 11 routinely recommended vaccines contain fewer than 130 pro-

TABLE 2. Number of Immunogenic Proteins and Polysaccharides Contained in Vaccines Over the Past 100 Years

1900		1960		1980		2000	
Vaccine	Proteins	Vaccine	Proteins	Vaccine	Proteins	Vaccine	Proteins/ Polysaccharides
Smallpox*	~200	Smallpox	~200	Diphtheria	1	Diphtheria	1
Total	~200	Diphtheria†	1	Tetanus	1	Tetanus	1
		Tetanus‡	1	WC-Pertussis	~3000	AC-Pertussis¶¶	2-5
		WC-Pertussis§	~3000	Polio	15	Polio	15
		Polio	15	Measles¶¶	10	Measles	10
		Total	~3217	Mumps#	9	Mumps	9
				Rubella**	5	Rubella	5
				Total	~3041	Hib††	2
						Varicella‡‡	69
						Pneumococcus§§	8
						Hepatitis B	1
						Total	123-126

* *Vaccinia* vaccine: Goebel SJ, Johnson GP, Perkus ME, et al. *Virology*. 1990;179:247-266.

† *Diphtheria* toxoid: *MMWR Morb Mortal Wkly Rep*. 1991 (August);40:1-28.

‡ *Tetanus* toxoid: *MMWR Morb Mortal Wkly Rep*. 1991 (August);40:1-28.

§ *Whole cell pertussis* vaccine: Number estimated from genome size. The sequence of *Bordetella pertussis* Tohama I strain will soon be completed at the Sanger Center in Great Britain.

¶ *Polio* vaccine: Wimmer E, Nomoto A. *Biologicals*. 1993;21:349-356; Kitamura N, Semler BL, Rothberg PG, et al. *Nature*. 1981;291:547-553; Five proteins per poliovirus virion and 3 poliovirus strains in the inactivated poliovirus vaccine (IPV).

¶¶ *Measles* vaccine: Griffen D, Bellini WL. *Measles virus*. In: Fields BN, ed. *Knipe DM, Howley PM, et al, eds. Philadelphia, PA: Lipincott-Raven Publishers; 1996.*

Mumps vaccine: Elango N, Varsanyi TM, Kovamees J, Norrby E. *J Gen Virol*. 1988;69:2893-2900.

** *Rubella* vaccine. Hofmann J, Gerstenberger S, Lachmann I, et al. *Virus Res*. 2000;68:155-160.

†† *Conjugate Haemophilus influenzae type b* vaccine: *MMWR Morb Mortal Wkly Rep*. 1991 (January);40:1-7.

‡‡ *Varicella* vaccine: Cohen JL. *Infect Dis Clin North Am*. 1996;10:457-468.

§§ *Streptococcus pneumoniae* vaccine: *MMWR Morb Mortal Wkly Rep*. 2000;49:1-29.

||| *Hepatitis B* vaccine: *MMWR Morb Mortal Wkly Rep*. 1991 (November);40:1-25.

¶¶¶ *Acellular pertussis* vaccine: *MMWR Morb Mortal Wkly Rep*. 1997 (March);46:1-25.

teins in total. Two factors account for this decline: first, the worldwide eradication of smallpox obviated the need for that vaccine, and second, advances in protein chemistry have resulted in vaccines containing fewer antigens (eg, replacement of whole-cell with acellular pertussis vaccine).

Children Respond to Multiple Vaccines Given at the Same Time in a Manner Similar to Individual Vaccines

If vaccines overwhelmed or weakened the immune system, then one would expect lesser immune responses when vaccines are given at the same time as compared with when they are given at different times.^{41,42} However, the following vaccines induce similar humoral immune responses when given at the same or different times: 1) MMR and varicella,^{43,44} 2) MMR, diphtheria-tetanus-pertussis (DTP), and OPV,⁴⁵ 3) hepatitis B, diphtheria-tetanus, and OPV,⁴⁶ 4) influenza and pneumococcus,⁴⁷ 5) MMR, DTP-Hib, and varicella,⁴⁸ 6) MMR and Hib,⁴⁹ and 7) DTP and Hib.⁴⁹

Achieving similar immune responses by giving vaccines at the same time at different sites may be more easily accomplished than by combining vaccines in the same syringe. Challenges to giving many vaccines in a single injection are based partly on incompatibilities of agents used to buffer or stabilize individual vaccines.⁵⁰

DO VACCINES "WEAKEN" THE IMMUNE SYSTEM?

Do Vaccines Increase the Risk of Other Infections?

Vaccines may cause temporary suppression of delayed-type hypersensitivity skin reactions or alter certain lymphocyte function tests in vitro.⁵¹⁻⁵⁷ How-

ever, the short-lived immunosuppression caused by certain vaccines does not result in an increased risk of infections with other pathogens soon after vaccination. Vaccinated children are not at greater risk of subsequent infections with other pathogens than unvaccinated children.⁵⁸⁻⁶⁰ On the contrary, in Germany, a study of 496 vaccinated and unvaccinated children found that children who received immunizations against diphtheria, pertussis, tetanus, Hib, and polio within the first 3 months of life had fewer infections with vaccine-related and -unrelated pathogens than the nonvaccinated group.⁶¹

Bacterial and viral infections, on the other hand, often predispose children and adults to severe, invasive infections with other pathogens. For example, patients with pneumococcal pneumonia are more likely to have had a recent influenza infection than matched controls.⁶² Similarly, varicella infection increases susceptibility to group A β -hemolytic streptococcal infections such as necrotizing fasciitis, toxic shock syndrome, and bacteremia.⁶³

SUMMARY

Current studies do not support the hypothesis that multiple vaccines overwhelm, weaken, or "use up" the immune system. On the contrary, young infants have an enormous capacity to respond to multiple vaccines, as well as to the many other challenges present in the environment. By providing protection against a number of bacterial and viral pathogens, vaccines prevent the "weakening" of the immune system and consequent secondary bacterial infections occasionally caused by natural infection.

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POSTDOC TRAIL LONG AND FILLED WITH PITFALLS

“The annual number of doctorates awarded in science nationwide has greatly outpaced the growth in the number of faculty jobs over the last 20 years . . . What used to be 2 or 3 years of career development often becomes 5 or more years in one post after another. Many of the postdocs are almost 40 before they start their first permanent positions and begin saving for retirement . . . The bottleneck means that the number of university postdocs in science and engineering has grown to an unprecedented size, doubling from 1981 to 1998, to 39,000, with most of that growth in the life sciences . . . In November 2000, the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine issued a report that said it was in the long-term interests of American science for postdocs to get better treatment . . . ‘It’s really unfortunate that people spend all these times in all these temporary positions and that they are 35 or 40,’ said Dr Walter T. Schaffer, a research training officer at the National Institutes of Health. ‘To some extent it discourages very bright people from entering science.’”

Lee J. *New York Times.* August 21, 2001

Noted by JFL, MD

Addressing Parents' Concerns: Do Multiple Vaccines Overwhelm or Weaken the Infant's Immune System?

Paul A. Offit, Jessica Quarles, Michael A. Gerber, Charles J. Hackett, Edgar K. Marcuse, Tobias R. Kollman, Bruce G. Gellin and Sarah Landry

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